fused amounts reached 0.3–3.0 mg/kg. In rabbits with intact circulation (IC) acebutolol induced a significant decrease in heast rate; no significant effects upon mean blood pressure and peripheral resistance (table), and aortic blood flow were observed. By contrast, in all animals under TCB (at constant arterial reinjection frequency) we noted a decrease in mean blood pressure and peripheral resistance (table); aortic blood flow did not change significantly.

A progressive increase in baroreceptor activity occurred immeciately after the start of infusion of acebutolol in all experiments (IC or TCB). Reductions in renal nerve activity were observed during infusion of acebutolol in rabbits with IC ($-27.0\pm2.3\%$; $n=3$ animals).

Discussion. The present experiments show that acute i.v. administration of acebutolol in rabbits induced an increase in baroreceptor firing and decreased postganglionic sympathetic renal-nerve discharge. Blood pressure and calculated peripheral resistance were reduced under TCB in contrast with the results obtained in rabbits with IC. The increase in peripheral resistance observed under IC in some animals might result from a reflex response to the reduced cardiac output. This interpretation could be consistent with our findings in TCB experiments, where a decrease in peripheral resistance was constantly noted after drug.

Sympathetic renal nerve activity was reduced by acebutolol. Similar results were obtained with β_1- β_2- adrenoceptor-blocking agents[2–4] and with another β_1-adrenoceptor-blocking agent, atenolol[5].

As observed with β_1- β_2-adrenoceptor-blocking agents, aortic baroreceptor firing was increased by acebutolol (and by atenolol; unpublished experiments) in spite of a diminished blood-pressure level. This increase in baroreceptor discharge was probably not caused by the vasodilation, which was not observed in all experiments. It is conceivable that the drug-induced change in aortic nerve activity could be due to an indirect effect mediated via central nervous effects on sympathetic nerve activity to the receptor area. Another possibility would be that inhibition of beta-adrenergic tone by the drugs leads to some contraction of aortic smooth-muscle cells, mimicking the effects of sympathetic activity and noradrenaline upon the baroreceptor area.

In conclusion it is noteworthy that all the β-adrenoceptor-blocking agents studied (with common antihypertensive properties but with different pharmacological patterns) induced an increase in baroreceptor activity. This phenomenon may initiate or contribute to the reduction in sympathetic outflow described at the splanchnic[6,7] and at the post ganglionic[2–5] levels.

Haemodynamic and baroreceptor responses to i.v. infusion of acebutolol (mean ± SEM)

	Intact circulation	Total cardiopulmonary by-pass
Heart rate in	-17.7 ± 4.7	0
beats/min	$n=7$	
(%)	$p<0.001$	
Mean blood	-6.0 ± 7.8	-8.8 ± 3.5
pressure	$n=7$	$n=5$
(mm Hg)	NS	$p<0.01$
Peripheral	$+4.0\pm22.1$	-15.8 ± 4.9
resistance in AU	$n=4$	$n=5$
(%)	NS	$p<0.01$
Baroreceptor activity	$+19.9\pm4.2$	$+14.4\pm9.9$
in counts/sec	$n=7$	$n=5$
(%)	$p<0.001$	$p<0.05$

n: Number of animals, NS: not significant, AU: arbitrary units.

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Embryotoxicity and teratogenicity of Cis-diamminedichloroplatinum

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Summary. Cis-diamminedichloroplatinum has lethal, toxic and teratogenic effects on presomitic mouse embryos in doses that are not toxic to adult animals.

Cis-diamminedichloroplatinum (II) (DDP) is a new antitumor compound that has shown promising effects in preclinical and clinical trials[1]. In addition to tumoricidal effects DDP has antimicrobial, immunosuppressive and mutagenic properties. In this paper we report that DDP is also extremely embryotoxic and teratogenic in the mouse.

Material and methods. Timed-pregnant outbred Swiss Webster mice were injected i.p. with freshly dissolved DDP on day 8 of pregnancy. The day the vaginal plug was found was considered to be day 1. Animals were injected with DDP in a single dose of either 13, 8 or 3 mg/kg b.wt. Control animals were either not injected at all or injected with 0.5 ml of saline. Pregnant dams were sacrificed on the 18th day of pregnancy. The numbers of live and stillborn fetuses and early and late resorptions were recorded. Each fetus was weighed. All the fetuses were examined under a dissecting microscope. Every third fetus was fixed in ethanol, cleared in glycerol and stained with alizarin red S for detection of skeletal anomalies. The experimental data were analyzed by use of Student's t-test.

Results. The data on embryotoxicity of DDP are summarized in the table. No maternal death was observed in any of the experimental groups. The live fetuses born to DDP treated dams weighed less than the controls despite the fact that each pregnant uterus contained fewer viable fetuses and that this could have caused more weight gain in

Embryotoxicity of DDP in Swiss Webster mice

Group	No. of dams	No. of conceptuses per animal	No. of resorbed/dead fetuses/animal	No. of live fetuses per animal	Total No. of resorbed or dead fetuses	Total No. of live fetuses	B.wt of live fetuses (g)
Noninjected	12	9.58±1.73	0.50±1.00	9.08±1.68	6	109	1.24±0.16
Saline injected	12	11.08±1.78	0.67±0.65	10.42±1.88	8	125	1.17±0.16
13 mg/kg DDP	10	9.90±1.20	9.90±1.20*	0	101*	0*	0
8 mg/kg DDP	13	9.77±2.92	9.54±3.10*	0.23±0.83*	124*	3*	0.80±0.08*
3 mg/kg DDP	12	10.67±1.72	3.33±4.03**	7.33±3.11**	40*	88*	1.09±0.18**

DDP was injected i.p. on day 8 of gestation. Control dams received saline or were not injected at all. All dams were killed on day 18 of gestation. Results are given as means±SD. * Statistically significant ($p < 0.001$). ** Statistically significant ($p < 0.01$).

the surviving embryos compared with the controls. A total of 30 fetuses from 12 dams injected with 3 mg/kg of DDP were examined after alizarin S staining. 11 dams had at least 1 malformed fetus. 19 out of the 30 fetuses examined showed some skeletal malformations such as zig-zag sternebrae, supernumerary ribs and vertebral malformations. 1 fetus showed multiple abnormalities including cleft palate and deformed extremities. Both live fetuses delivered from dams treated with 8 mg/kg DDP showed skeletal malformations. In the control group only 1 fetus showed grossly visible malformations of extremities. 1 of 22 alizarin S stained fetus showed zig-zag sternebrae. No other skeletal malformations were noted in untreated animals.

Discussion. LD_{50} for DDP injected i.p. was estimated to be in the range of 7.6 to 9.5 mg/kg for rodents[2]. The newer, better purified compounds seem to be less toxic. Our data (unpublished) indicate that LD_{50} for Swiss Webster mice injected i.p. is in the range of 17–18 mg/kg. Attesting to the relatively low toxicity of new compounds is the fact that in this study, none of the dams injected with either 3,8 or 13 mg/kg died. Doses of 9 mg/kg seem to be well-tolerated even after multiple injections[3]. In contrast to low toxicity in adult animals DDP appears to be highly embryotoxic if administered during early stages of pregnancy. Even in a dose of 3 mg/kg, DDP kills approximately 50% of all exposed fetuses. The surviving fetuses show weight reduction and skeletal malformations. Although most skeletal malformations were minor, their presence indicates that DDP interferes with normal embryogenesis and that its use in pregnant women should be discouraged.

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Hypertrophie du foie provoquée par l'oxythioquinox: Influence du taux de lipides de la ration alimentaire

Liver enlargement induced by oxythioquinox: Effect of the fat content of the diet

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Summary. The relationship between the level of lipid calories in the diet and the effects of oxythioquinox, administered at 200 mg/kg fresh food, for 35 days, wa studied on the liver enlargement of rat. The results show that the level lipid calories itself have no effect since, in the treated animals, the liver enlargement is due part to an increase of the water content and part to an increase of the size of the cells.

L'augmentation du poids du foie sous l'effet des substances xénobiotiques et en particulier des pesticides est un phénomène fréquemment observé en toxicologie[1-3]. Certains auteurs[4,5] ont observé une augmentation importante du poids du foie chez les animaux intoxiqués à l'oxythioquinox, dérivé à la fois fongicide et acaricide[6,7], sans toutefois en préciser les causes. Dans un travail antérieur[8], nous avions observé que cette augmentation du poids du foie, sous l'effet de l'oxythioquinox administré à 200 mg/kg d'aliment, était en relation avec le taux de calories lipidiques du régime. Il nous a donc paru intéressant de préciser la nature de cette hépatomégalie et de rechercher une intéraction éventuelle entre les effets de l'oxythioquinox et ceux des lipides du régime puisque nous avions également montré que la toxicité de l'oxythioquinox était potentialisée lorsqu'il était administré en solution huileuse[9].

Matériel et méthodes. Nous avons utilisé des rats mâles (Wistar CF), répartis en 4 lots de 6 rats témoins et 4 lots de 6 rats traités, en fonction des calories lipidiques de la ration, les traités recevant l'oxythioquinox, solubilisé dans les lipides de la ration, à la concentration de 200 mg/kg d'aliment frais. Les régimes dont la composition a été donnée dans un travail antérieur[10] contiennent respectivement 3, 18, 35 et 49% de calories d'origine lipidiques. En faisant varier le taux d'hydratation et la teneur en glucides, nous avons maintenu le rapport calories totales/poids des protéines en g, constant et égal à 21, l'apport calorique total du régime étant de 1950 cal/kg d'aliment frais. A la fin des 35 jours de la période expérimentale, les animaux ont été pesés, sacrifiés et le foie prélevé. Sur cet organe, nous avons déterminé la teneur en eau (105 °C pendant 48 h), les protéines[11], l'ARN et l'ADN[12], les acides gras totaux et le cholestérol[13]. Sur ces résultats, nous avons étudié successivement la régression, la linéarité, l'effet propre du régime, l'effet propre de l'oxythioquinox par comparaison des ordonnées à l'origine et l'intéraction.par le test de compa-